REMARKS

The specification has been amended to correct the claims of priority to the previously filed application from which this application was intended to take priority. Support is found in the common lineage of all applications cited.

The specification has also been amended to provide written support for the subject matter claimed herein. Support is found in the priority application 08/691,794, which was pending at the time of entry of the presently claimed subject matter. The previous amendment to the claims necessitates a change in inventorship. Applicants will submit a new executed declaration, once the application and claims have been reviewed by the inventors and the declaration has been signed.

Claims 15 and 18-33 are now pending in the application. Claims 16 and 17 have been cancelled without prejudice or disclaimer. Claims 15, 18 ans 21 have been amended for clarity.

A "clean" version of amendments to the specification and the amended claim set are presented above. Amendments to the claims and specification are indicated in the section entitled "Version Showing Changes Made", which follows these remarks.

Rejection under 35 U.S.C. §101

Claims 19-21, 23, 25, 27, 29-32 are rejected under 35 U.S.C. §101 as directed to non-statutory subject matter. The Examiner stated that bovine VEGF also differs from the "native VEGF" in one of the amino acids, thus naturally occurring bovine VEGF is also included in our claims. Because the claims do not show the hand of man involved in the invention, they are unpatentable. Applicants respectfully traverse.

As the Examiner has suggested, the proper test for patentable subject matter is whether the claimed matter is the result of human intervention. (See M.P.E.P. §2105). Claim 19 is directed to a nucleic acid encoding a polypeptide comprising a VEGF variant of native VEGF, wherein at least one of a list of amino acids of native VEGF is modified

to form said variant. Modification by definition involves human manipulation of the VEGF sequence, which includes, for example, DNA mutatagenesis (see e.g., pages 19-21). Applicant thus respectfully submit that human intervention is involved in the present claim and request that the rejection of claim 19 be withdrawn.

For the same reason as discussed above, dependent claims 20-21, 23, 25, 27, and 29-32 are also patentable. Therefore Applicants respectfully request that this rejection be withdrawn.

Rejection under double patenting

Claim 18 is rejected under the judicially created doctrine of double patenting over claim 1 of U.S. Patent No. 6,057,428 (the '428 patent). Claim 15 is rejected under the judicially created doctrine of obvious-type double patenting as being unpatentable over claim 1 of the '428 patent.

Without necessarily agreeing with the propriety of the rejection, Applicants will consider submitting a terminal disclaimer to the '428 patent, upon the finding of otherwise patentable subject matter, if the rejected claims are not amended and the double patenting rejections are maintained. While there is still the possibility that the present claims may be amended, Applicants request that this rejection be held in abeyance until such time as it is deemed necessary for a terminal disclaimer to be filed.

Rejection under 35 U.S.C. §112, second paragraph

Claim 18 and its dependent claim 15 are rejected under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully traverse.

Applicants do not agree with the Examiner's assessment that since a composition must comprise more than one element, more than one element must be recited in the claim. The requirement of 35 U.S.C. § 112, second paragraph is that the person of ordinary skill in the art should understand the meaning of the claim. Applicants submit that the skilled artisan in the present field understands that a composition comprises more than one

element, therefore, recitation of additional elements is not required. However, in the interest of expediting prosecution, Claim 18 has been amended to recite the additional element of "a carrier", as suggested by the Examiner.

Claim 21 and its dependent Claim 22 are found to be indefinite because it is not clear how "at least one" (claim 19) is different from "one or more" (claim 21) of said amino acids is modified. Applicant has accordingly amended claim 21 to change "one or more" to "two or more".

Applicant respectfully submit that Claims 18 and 21 and their dependent claims now conform to the Examiner's requirement and request that these rejections be withdrawn.

Rejection under 35 U.S.C. §112, first paragraph

Claims 19-33 are rejected under 35 U.S.C. §112, first paragraph lacking written support for modifications of residues Phe 17, Ile 46, Ile 43. Applicants respectfully traverse.

The specification has been amended at page 5, line 4, to recite modification of the residues specified in the claims. Applicants submit that the specification provides written support for Claims 19-33 and respectfully requests withdrawal of this rejection.

Claims 18 and 15 are rejected under 35 U.S.C. §112, first paragraph because the specification does not provide enablement for VEGF variants that contain deletions or insertions in the KDR or FLT-1 region, and variants that differ in amino acid sequence from native VEGF outside of those regions.

The requirement of enablement demands that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). A patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991).

In making the rejection, the Examiner has two major concerns. First, it is not clear which amino acids outside of the binding regions can be altered, and how the alteration of those amino acids can affect binding affinity. Second, because the claimed variants include deletions and insertions that might abolish the overall characteristics of VEGF, the claims are overly broad and have not been enabled by the specification. Applicant hereby respectfully address each of the Examiner's concerns.

With regard to the Examiner's first concern, Applicants respectfully draw the Examiner's attention to page 16 of the specification, where we disclosed that point mutational or other broader variations may be made in regions of VEGF outside of KDR or FLT-1 so as to impart interesting properties that do not affect the overall properties of the variants with respect to the KDR or FLT-1 regions (page 16, ll. 23-28). General methods of making amino acid modifications have been disclosed (see, for example, pages 19-21 and pages 38-39). We have also disclosed assays that will allow one to evaluate the level, activity, and binding to KDR or FLT-1 receptors of the produced VEGF variants (page 24, ll.15-24). With these teachings, any person skilled in the art will be able to produce the above-mentioned VEGF variants, i.e., VEGF variants which differ in amino acid sequence from native VEGF in areas outside the KDR or FLT-1 region. The invention is production of VEGF variants with modified binding to KDR or FLT-1 receptors, the variants have modification in the KDR binding region or the FLT-1 binding region. Applicants do not attempt to claim all VEGF variants with modified binding, only those with modifications to the specified binding regions. Applicants have clearly shown that modification to these binding regions modifies the binding to the receptors, and has a right to claim such variants. It is not proper for the Examiner to attempt to open the door for easy avoidance of infringement by making a simple conserved modification of the molecule outside of the KDR and/or FLT-1 binding regions, along with the modifications as claimed. Requiring specifying which residue may be modified which do not alter binding to KDR or FLT-1 receptors acts to read limitations into the claims. The required limitations are those recited. The affect of further modifications, not required by the claims, are easily determined by routine screening, as described in the specification screening.

With regard to the Examiner's second concern, Applicant respectfully draw the Examiner's attention to page 23 of the specification where the possibility that deletion, insertion, and substitutions might produce radical changes in the characteristics of the VEGF molecule is addressed. Applicants teach that the effect of the modifications can be evaluated by routine screening assays. For example, desired variants can be made by purifying them through a rabbit polyclonal anti-VEGF column to absorb the variant by binding it to at least one remaining immune epitope. It is not necessary to disclose whether insertions or deletions within the binding regions can alter binding, because it will become apparent after the mutagenesis and screening as taught by the present invention.

Applicants submit that the claims are only so broad as to cover the subject matter rightfully claimed by the Applicants. The claimed VEGF variants are still VEGF molecules, and are only encompassed by the claims if they are modified as claimed. The modifications required by the claims are clearly enabled by the specification. Applicants submit that the present claims are consistent with standard claim construction for similar subject matter, as exemplified by the claims of the issued '428 patent and U.S. Patent No. 6,020,473.

In light of the discussion above, Applicants submit that Claims 18 and 15 satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. Therefore, Applicants respectfully request withdrawal of this rejection.

Rejection under 35 U.S.C. §102(b)

Claim 18 is rejected as being anticipated by Tischer et al. Applicants respectfully traverse.

Tischer et al. teaches the amino acid sequence of human and bovine VEGF.

Claim 18 claims a composition of matter comprising a purified polypeptide comprising a VEGF variant, which contains at least one modification in the KDR and/or FLT-1 region such that the binding affinity of said region(s) is modified with respect to binding affinity of KDR and/or FLT receptors with native VEGF.

In order to anticipate a claim, the prior art must disclose "each and every claim" of the claimed invention. *SSIH Equipment S.A. v. U.S. Inc. Int'l. Trade Commission*, 218 USPQ 678, 688 (Fed. Cir. 1983).

Tishcher et al. does not teach a VEGF variant that contains at least one modification in the KDR and/or FLT-1 region . As discussed above, "modification" connotes active manipulation by man to produce the change. Tischer neither teaches not suggests modification of the KDR or FLT-1 binding regions. Without teaching this elelment of the claim, Tischer cannot anticipate Claim 18.

In light of the discussion above, Applicants submit that Claim 18 is not anticipated by Tischler. Therefore, withdrawal of this rejection is respectfully requested.

Rejection under 35 USC §103

Claim 15 is rejected under 35 U.S.C. §103(a) as being obvious over Tischer et al.

Tischer et al. teaches a conditioned medium containing secreted human VEGF protein. It also teaches bovine VEGF protein, as discussed above.

Claim 15 is directed to a composition matter that comprising the VEGF variant of Claim 18 (discussed above) and a pharmaceutically acceptable carrier.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestions or motivation, wether in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or reference when combined) must teach or suggest all the claim limitations. (see M.P.E.P. §2143).

Tischer et al. does not teach or suggest a composition of matter containing a VEGF variant having a modification in the KDR or FLT-1 binding domain, as discussed above. Therefore, a suggestion to modify the KDR or FLT-1 binding region cannot be gleaned from Tischer. Without any teaching of such a modification, no reasonable expectation of success in obtaining the presently claimed VEGF variants can be had.

For the above reasons, Applicants respectfully submit that a *prima facie* case of obviousness has not been established with the present invention, and respectfully request withdrawal of this rejection.

CONCLUSION

Applicants respectfully submit that the claims are now in condition for allowance and early notification of such is earnestly solicited. If, upon review, the Examiner feels there are additional outstanding issues which may be resolved by telephone, the Examiner is invited to call the undersigned attorney at (415) 781-1989.

Respectfully submitted,

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VERSION SHOWING CHANGES MADE

IN THE SPECIFICATION:

The first paragraph after the heading "Cross-Reference to Related Applications" at page 1, line 4, as amended by the transmittal accompanying the present application, has been replaced with the following paragraph:

--This is a continuation-in-part application of application Serial No. 08/567,200 filed December 5, 1995, now Patent No. 6,020,473 which issued February 1, 2000 and a continuation-in-part of application Serial No. 08/691,794 filed August 2, 1996, now Patent No. 6,057,428 which issued May 2, 2000, and claims the benefit of provisional application No. 60/002,827 filed August 25, 1995.--

The following paragraph has been inserted at page 5, line 4:

--In yet another embodiment of the invention, mutagenensis is effected at positions Phe 17, Ile 43 and/or Ile 46.--

IN THE CLAIMS:

15. (Twice Amended) The composition of matter of Claim 18, [further comprising] wherein said carrier is a pharmaceutically acceptable carrier.

Claims 16 and 17 have been cancelled without prejudice or disclaimer.

18. (Amended) A composition of matter comprising a purified polypeptide, said polypeptide comprising:

a) a vascular endothelial cell growth factor (VEGF) variant of native VEGF wherein said variant differs from native VEGF in that said variant contains at least one modification in the Kinase domain region (KDR) and/or FMS-like Tyrosine Kinase region (FLT-1) such that the binding affinity of said region(s) is modified with respect to binding affinity of KDR and or FLT-1 receptor(s) with native VEGF; and

b) a carrier.

21. (Amended) The nucleic acid according to Claim 19 wherein [one] two or more of said amino acids is modified.